Prognostic Significance of B-type Natriuretic Peptide in Patients with Left Ventricular Thrombus

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Research

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Abstract

Background: There is sparse information on the prognostic value of B-type natriuretic peptide (BNP) for the outcomes in patients with left ventricular thrombus (LVT). We aimed to determine the prognostic value of BNP in LVT.

Methods: Patients diagnosed with LVT by transthoracic echocardiography between November 2009 to July 2020 at our institution were included. The endpoints were all-cause mortality and systemic embolism.

Results: Ninety-two subjects were finally included in the study. The mean age of the cohort was 56.73±14.12, and 80.4% of the patients were male. The median BNP (1st quartile- 3rd quartile) was 437.5 (112.74-1317.5). The total all-cause mortality rate was 30.44% (28/92), and the 1-year, 2-year and 3-year cumulative survival rates were 85.4%, 75.5% and 66.5% respectively. Systemic embolism was identified in 10 subjects. COX multivariate analysis showed that Log BNP (HR, 4.96; 95%CI, 2.03-12.13; P=0.000) and LV posterior thickness (HR, 0.71; 95%CI, 0.51-0.97; P=0.034) were significantly associated with all-cause mortality. In addition, patients with BNP levels in the upper median (≥ 437.5pg/ml) had significantly higher all-cause mortality rate compared to those with lower median BNP (<437.5pg/ml; P=0.004). The area under the receiver operating characteristic curve for BNP and all-cause mortality was 0.71. In the linear trend test, BNP quartiles were significantly related to all-cause mortality in all models, and the P values for trend in models 1, 2 and 3 were 0.005, 0.006 and 0.048 respectively.

Conclusion: BNP level is a prognostic factor for all-cause mortality in LVT patients, and elevated BNP is indicative of a higher risk of LVT.

Introduction

Left ventricular thrombus (LVT) is a complication of systolic dysfunction, and usually afflicts patients with myocardial infarction or dilated cardiomyopathy. Both ischemic and non-ischemic LVT formation follow the Virchow's triad including reduced ventricular wall motion, endomyocardial injury and hypercoagulability/ stasis of blood flow [1, 2]. Despite primary percutaneous coronary intervention (PCI) and the significant scientific breakthrough beyond foundational neurohormonal therapies improving the prognosis of heart failure (HF) in recent decades, patients with LVT are at a higher risk of cardioembolic stroke, systemic embolization and all-cause death [3], and the cumulative incidence of thromboembolism and mortality is as high as 20% [4]. Nevertheless, little is known regarding risk stratification in LVT, which warrants identification of novel prognostic biomarkers.

B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are reliable diagnostic and prognostic biomarkers for HF patients [5], and are routinely used to assist diagnosis, risk stratification and treatment optimization. The peptides are mainly secreted by the left ventricle cardiomyocytes in response to ventricular stretch due to cardiovascular stress [6]. High levels of BNP correlate with reduced left ventricular ejection fraction (LVEF), ventricular wall hypokinesis and akinesis

[7]. In addition, studies show that patients with reduced LVEF or decreased ventricular wall motion are at a higher risk of developing LVT [8–10]. A study on 143 patients free of atrial fibrillation while with old myocardial infarction revealed that BNP and left ventricle segment asynergy were associated with cardioembolic stroke [11]. Based on these findings, we hypothesized that the BNP level is a potential marker of LVT prognosis, and therefore retrospectively analyzed its prognostic and predictive value in patients with LVT.

Methods

Study population

Patients diagnosed with LVT by transthoracic echocardiography (TTE) from November 2009 to July 2020 at the Xinqiao Hospital, Chongqing, China were enrolled for the study. The inclusion criteria were as follows: 1) LVT diagnosis by TTE, 2) age ≥ 18 years, and 3) availability of on-admission BNP or NT-pro BNP data. Patients with in-hospital mortality, cancer, non-compaction of the ventricular myocardium, tetralogy of fallot, past cardiac valve replacement, and coronary artery bypass grafting within 30 days were excluded. The study was approved by the Ethics Committee of the hospital, and was in accordance with the 1975 Declaration of Helsinki and its amendments. Given the retrospective study design, informed consent was waived.

Data collection and tests

The baseline characteristics were retrieved from the medical records. LVT was screened by non-contrast TTE and contrast TTE when necessary, and identified as an echo dense mass close to a hypokinetic or akinetic myocardial segment in more than two views [12]. The images were reviewed by two senior echocardiologists. BMI was calculated by dividing the body weight with the squared height. Hypertension was diagnosed as per previous standards due to the retrospective nature of the study [13]. Diabetes mellitus was diagnosed on the basis of fasting glucose > 126 mg/dl or prescription of hypoglycemic drugs. Dilated cardiomyopathy was defined by the presence of left ventricular or biventricular dilatation and systolic dysfunction excluding any known cause of myocardial disease [14]. Coronary heart disease (CHD) was confirmed by coronary artery computed tomography (CT), computed tomographic angiography (CTA) or percutaneous coronary angiography (PCA). All laboratory tests were conducted within 24h of admission after overnight fasting. BNP levels were measured using the Triage Fluorescence Immunochromatographic Assay kit (Huanzhong Biotech Co. Ltd., Shijiazhuang, China) and NT-pro BNP using the ChemiLuminescent Immunoassay assay kit (Hybiome Biomedical Engineering Co. Ltd., Suzhou, China). NT-proBNP was converted to BNP using the formula BNP = NT-pro BNP/8.03 in case of atrial fibrillation, or BNP = NT-pro BNP/5.75 in the absence of atrial fibrillation [15].

Endpoint and follow-up

The endpoints were all-cause mortality and systemic embolism. Survival and adverse events data were collected by office visits or telephone contacts with patients and their relatives. Loss to follow-up was

defined as the lack of response to telephone contacts in addition to non-availability of follow-up medical records.

Statistical analysis

Continuous variables are presented as mean ± standard variation, and the categorical variables as percentages (or frequencies). Two-sample T-test or non-parametric Mann–Whitney U test were used to compare continuous variables, while categorical variables between groups were compared by Fisher exact or $\chi 2$ test. Survival curves were plotted by the Kaplan-Meier method and compared by the log-rank test. The variables with $P < 0.10$ in the univariate analysis were subjected to multivariable Cox proportional hazards regression analysis by a backward conditional method. A linear trend test was performed by entering the median value for each category of BNP quartiles. The association between BNP and all-cause mortality was evaluated using area under the receiver operating characteristic (ROC) curve (AUC). Hazard ratio (HR) and 95% confidence interval (CI) for all-cause mortality were calculated by 1 unit increase in log transformed BNP. A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using Statistical Package for the Social Sciences version 25.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

Based on the study of 957,380 echocardiographic records, we identified 156 patients that were diagnosed with LVT by TTE, of which 92 were included in the study based on the inclusion and exclusion criteria (Fig. 1). The mean age of the cohort was 56.73 ± 14.12 years, and 80.4% were male. Twenty-eight patients died during the median follow-up period of 702 days. The median BNP (1st quartile- 3rd quartile) was 437.5 (112.74-1317.5). The baseline characteristics of the surviving and non-surviving patients are summarized in Table 1. The BMI, incidence of LV aneurysm, smoking, incidence of CHD, and the levels of albumin (ALB), high density lipoprotein cholesterol and triglycerides (TG) were significantly lower in the non-surviving group, whereas the incidence of dilated cardiomyopathy, white blood cell (WBC), neutrophil and monocyte counts and Log BNP level were significantly higher. No significant differences were seen in the other variables (Table 1).

Table 1
Baseline Characteristics at Admission of the LVT Patients.

Clinical characteristics	Total N = 92	Death Group N = 28	Survival Group N = 64	P value
Age, years	56.73 ± 14.12	59.96 ± 16.65	55.31 ± 12.74	0.194
BMI, kg/m^2	24.06 ± 2.96	22.92 ± 2.12	24.52 ± 3.13	0.021*
Gender (male)	74(80.4)	21(75.0)	53(82.8)	0.385
Current smoking	52(56.5)	10(35.7)	42(65.6)	0.008*
Co-morbidities				
Hypertension	40(43.5)	12(42.8)	28(43.7)	0.937
Dyslipidemia	15(16.3)	2(7.1)	13(20.3)	0.205
Diabetes mellitus	16(17.4)	3(10.7)	13(20.3)	0.413
DCM	18(19.6)	9(32.1)	9(14.1)	0.044*
CHD	74(80.4)	19(67.9)	55(85.9)	0.044*
LV aneurysm	39(42.4)	5(17.9)	34(53.1)	0.002*
Atrial fibrillation	4(4.3)	3(10.7)	1(1.6)	0.154
COPD	5(5.4)	4(14.3)	1(1.6)	0.983
Laboratory findings				
White cell count	8.13 ± 2.74	9.44 ± 3.45	7.55 ± 2.14	0.011*
Neutrophil count	4.94(4.0-6.51)	5.46(4.58–9.41)	4.8(3.54–5.46)	0.020*
Lymphcyte N	1.70 ± 0.69	1.58 ± 0.74	1.75 ± 0.66	0.257
Monocyte N	0.62 ± 0.26	0.76 ± 0.33	0.56 ± 0.21	0.002*
HB levels	141.34 ± 19.28	140.07 ± 15.39	141.9 ± 20.86	0.687
Platelet count	184(153–232)	200(156.5-263.5)	178(150–228)	0.256
CRP levels	5.0 (5.0–20.0)	9.35(5.43–49.48)	5.0 (5.0–20.0)	0.433
Creatinine	80.0(68.4-100.6)	82.0(67.6-106.3)	78.9(68.5–98.2)	0.788

Continuous values are documented by Mean ± SD or Median (1st quartile- 3rd quartile). Categorical variables are recorded by n (percentage). BMI: Body mass index; BNP: brain natriuretic peptide; CHD: Coronary heart disease; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DCM: Dilated cardiomyopathy; HDL-C: High density lipoprotein cholesterol; LA: left atrium; LDL-C: low density lipoprotein-cholesterol; LV: left ventricular; LVEF: left ventricular ejection fraction; SV: stroke volume; LVEDd: LV end-diastolic diameter; TG: triglycerides.

Clinical characteristics	Total N = 92	Death Group N = 28	Survival Group N = 64	P value
Cysteine	1.30 ± 0.98	1.34 ± 0.58	1.29 ± 1.09	0.055
Albumin	38.86 ± 4.69	36.86 ± 3.63	39.73 ± 4.85	0.006*
HDL-C	0.94 ± 0.22	0.85 ± 0.26	0.98 ± 0.19	0.032*
TG	1.57 ± 0.87	1.22 ± 0.64	1.71 ± 0.91	0.017*
LDL-C	2.46 ± 0.9	2.51 ± 0.97	2.44 ± 0.88	0.864
Log BNP level	2.55 ± 0.65	2.89 ± 0.52	2.4 ± 0.65	0.001*
Echocardiographic variables				
LA diameter, mm	39.09 ± 5.21	39.88 ± 5.64	38.74 ± 5.01	0.359
LVEDd, mm	56.77 ± 9.76	59.83 ± 12.01	55.43 ± 8.36	0.086
LVEF(%)	45.98 ± 14.29	41.45 ± 16.37	47.97 ± 12.91	0.069
SV (mL)	75.1 ± 17.51	70.95 ± 20.32	76.87 ± 16.02	0.167
LV posterior thickness	10.02 ± 1.28	9.7 ± 1.29	10.16 ± 1.267	0.092
Septum thickness	10.9 ± 1.68	10.47 ± 1.79	11.09 ± 1.55	0.147

Continuous values are documented by Mean ± SD or Median (1st quartile- 3rd quartile). Categorical variables are recorded by n (percentage). BMI: Body mass index; BNP: brain natriuretic peptide; CHD: Coronary heart disease; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DCM: Dilated cardiomyopathy; HDL-C: High density lipoprotein cholesterol; LA: left atrium; LDL-C: low density lipoprotein-cholesterol; LV: left ventricular; LVEF: left ventricular ejection fraction; SV: stroke volume; LVEDd: LV end-diastolic diameter; TG: triglycerides.

Outcomes

The all-cause mortality rate during the median follow-up duration of 702 days was 30.44% (28/92). The 1-year, 2-year and 3-year cumulative survival rates were 85.4%, 75.5% and 66.5% respectively. Ten subjects underwent systemic embolism, of which only 3 survived the complication.

COX proportional hazard model

Univariate analysis showed that BMI, WBC, platelet, ALB, Log BNP, LV diameter, LV posterior thickness, LVEF and septum thickness were significantly correlated to all-cause mortality. However, only Log BNP (HR, 4.96; 95%CI, 2.03–12.13; P = 0.000) and LV posterior thickness (HR, 0.71; 95%CI, 0.51–0.97; P = 0.034) were identified as the independent risk factors in the multivariate analysis (Table 2). As shown in Fig. 2A, patients with BNP levels in the upper median (≥ 437.5pg/ml) showed significantly higher mortality rate (P = 0.004) compared to those with BNP level in the lower median (< 437.5pg/ml).

Table 2
Backward Conditional Cox Univariate and Multivariate Analysis for All-cause Mortality.

	Univariate	**Multivariate**			
	P value	HR	Lower limit	Upper limit	P value
BMI	0.031	0.86	0.73	1.01	0.065
WBC	0.007	-	-	-	-
PLT	0.039	-	-	-	-
ALB	0.013	-	-	-	-
Log BNP	0.002	4.96	2.03	12.13	0.000
LV diameter	0.011	-	-	-	-
LVPW thickness	0.082	0.71	0.51	0.97	0.034
LVEF	0.038	-	-	-	-
Septum thickness	0.047	-	-	-	-

ALB: albumin; BMI: body mass index; BNP: brain natriuretic peptide; LV: left ventricle; LVEF: left ventricular ejection fraction; LVPW, LV posterior wall; PLT: platelet; WBC: white blood cell count.

ROC curve

The ROC curve depicting the relationship between BNP and all-cause death is shown in Fig. 2B. The AUC for BNP was 0.71 and the cut-off point was 667pg/ml. The corresponding sensibility, specificity and Youden index were 0.71, 0.72 and 0.43 respectively.

Linear trend test

The BNP levels were divided into four quartiles to test the prognostic value. As shown in Table 3, Model 1 was adjusted for age, gender and BMI, Model 2 for age, gender, BMI, WBC, platelet and ALB, and Model 3 for age, gender, BMI, WBC, PLT, ALB, LV diameter, LV posterior thickness, LVEF and septum thickness. BNP quartiles were significantly related to all-cause mortality in all models. The P for trend values for models 1, 2 and 3 were 0.005, 0.006 and 0.048 respectively, and the HRs and 95%CIs were 8.72 (1.70-102.57), 6.67 (0.84–53.14) and 13.61 (1.61-114.98) respectively (Table 3).

Table 3
Adjusted Hazard Ratios and 95% Confidence Interval for BNP by Quartiles on All-cause Mortality.

	BNP				
	Q1	Q2	Q3	Q4	P for trend*
	n = 23	n = 23	n = 23	n = 23	
Median pg/ml	60.8	190.0	926.0	1830.0	
Model 1	1(reference)	2.39(0.27–21.66)	13.2(1.70-102.57)	8.72(1.70-102.57)	0.005
Model 2	1(reference)	1.70(0.18–15.81)	9.87(1.27–77.52)	6.67(0.84–53.14)	0.006
Model 3	1(reference)	2.39(0.27–22.25)	14.45(1.85-112.76)	13.61(1.61-114.98)	0.048

HRs and 95%CIs were calculated by Cox proportional hazards regression models by backward conditional method; *P for trend was gained by entering the median value of each category of BNP quartiles; Model 1 adjusted for age, gender, and body mass index; Model 2 adjusted for age, gender, body mass index, WBC, PLT, and ALB; Model 3 adjusted for age, gender, body mass index, WBC, PLT, ALB, LV diameter, LV posterior thickness, LVEF, and Septum thickness.

ALB: albumin; BNP: brain natriuretic peptide; EF: ejection fraction; LV: left ventricle; LVEF: left ventricular ejection fraction; PLT: platelet; Q: quartiles; WBC: white blood cell count.

Subgroup analysis

Further, we analyzed the predicative value of BNP in the CHD subgroup. The patient with BNP levels in the upper median showed significantly higher mortality rate than that in the lower median group (P = 0.011). Consistently, significant differences were observed for BNP levels with regard to all-cause mortality in Kaplan–meier analysis (P = 0.004; see **additional file 1**).

Discussion

We retrospectively analyzed the predisposing factors that affect cardiovascular events and mortality in LVT patients, and found that higher BNP levels were associated with increased risk of all-cause mortality.

A previous retrospective review of more than 80,000 medical records revealed that the incidence of LVT is 7 per 10,000 patients [16]. Another observational study identified 128 patients with LV thrombus from 140,636 echocardiograms [4]. Consistent with these reports, the incidence of LVT was also low in our study and only 156 patients were recruited after screening more than 957,000 echocardiographic records. While PCI has markedly reduced the incidence of post-myocardial infarction LVT, cases related to heart failure have increased. Around 2/3rd of the patients in our cohort were diagnosed with CHD and the rest with dilated cardiomyopathy. The etiology of LVT patients evolves. One study showed that 80% of LVT

cases are ischemic [16], and Bhatt *et al* showed that de novo HF (38%) was more frequently associated with LVT compared to acute MI (25.9%) [4]. This discrepancy may be due to the bias of small LVT population, or the different criteria utilized by the studies to analyze the precipitating factor of LVT.

Despite its low incidence rate, LVT is a lethal complication of MI or HF and is associated with high rates of systemic embolism, morbidity and mortality. We observed 10 cases of systemic embolism during the follow-up, which is similar to the reported 2–3% for PCI. Early revascularization can attenuate left ventricular dysfunction and therefore decrease the risk for LVT and associated embolism. Furthermore, anticoagulation therapy resolves the thrombus and further lowers the SE incidence to 1.9% within a year [4]. In addition, Maniwa *et al* reported a high incidence (16.3%) of SE in AMI patients with LVT [17], which can be attributed to the statistical variations in the incidence of LVT, longer follow-up period and lower primary PCI rate.

LVT patients are usually at a very high risk of developing major adverse cardiovascular events (MACE), including embolic or major bleeding complications, as well as death. A retrospective study of 159 LVT patients screened from 90,065 echocardiograms reported that MACE and all-cause mortality occurred in 37.1% and 18.9% of the patients respectively within a median follow-up period of 632 days [18]. Likewise, another study reported in-hospital mortality of 7.8% and post-discharge one-year mortality rate of 13% among LVT patients [4]. In this study, we followed up the patients for 702 days and detected mortality rate of 30.44%. These findings collectively show the poor prognosis of LVT. Although PCI and adjunctive therapy have improved the outcome of LVT, it is crucial to identify the high-risk patients through appropriate predictive markers.

BNP is a diagnostic biomarker of HF, and its high levels are associated with poor prognosis of HF patients. MI frequently leads to ventricular dysfunction and HF, which is accompanied by BNP elevation. In our study as well, BNP was the most potent predicator of all-cause mortality of LVT patients, and elevated BNP correlated to greater risk of death. Anti-coagulation therapy is recommended to LVT patients if not contraindicated according to several guidelines. The current ESC guidelines recommend 6 months as the minimum duration of anticoagulation therapy [19]. However, prolonged anti-coagulation may benefit patients with recurrent and late LVT formation. The outcomes of HF patients have improved markedly in recent years due to drugs that inhibit or even reverse cardiac remodeling. Thus, beta-blockers, angiotensin receptor neprilysin inhibitor (ARNI) and sodium-glucose cotransporter (SGLT)2 inhibitors should be initiated in patients with elevated BNP.

The study has several limitations that ought to be considered. This was a retrospective study conducted on a single center cohort, although a large number of medical records screened. Second, echocardiography was used to diagnose LVT, which might be not be as sensitive or specific as cardiac magnetic resonance imaging for detecting LVT formation. Third, the sample size was small due to the low incidence of LVT, which may have limited identification of other potential risk factors. Finally, the results of this observational study should be considered exploratory rather than definitive.

Conclusion

Elevated BNP is associated with a higher risk for all-cause mortality in patients with LVT, and those with BNP levels > 667pg/mL have significantly worse outcomes. Therefore, it is crucial to measure natriuretic peptide levels in the high-risk cohort.

Abbreviations

ALB
albumin
BMI
Body mass index
BNP
brain natriuretic peptide
CHD
coronary heart disease
COPD
chronic obstructive pulmonary disease
CRP
C-reactive protein
CTA
computed tomographic angiography
HDL
High density lipoprotein
LA
left atrium
LVEF
left ventricular ejection fraction;
LDL-C
low density lipoprotein- cholesterol
LVT
left ventricular thrombus
PCI
percutaneous coronary intervention
PLT
platelet;
SV
stroke volume
TG
triglycerides

WBC
white blood cell count

Declarations

Acknowledgments

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Authors' contributions

Z.A., Z.G., and Z.Q. were involved in conception and design. Z.A., Z.G., C.H., L.W., and L.Z. helped in acquisition of data. Z.A., Z.G., and Z.Q. contributed to interpretation of data. C.L., R.R., and S.G. contributed to review of ultrasonic data. Z.A., Z.G., and Z.Q. were involved in statistical analysis. Z.A., Z.G., and Z.Q. helped in drafting of the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content. Z.A., Z.G., C.H., and Z.Q. were involved in final revision of manuscript. Z.Q. helped in study supervision. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the hospital, and was in accordance with the 1975 Declaration of Helsinki and its amendments. This was a retrospective study based on the medical records; therefore, informed consent was waived.

Consent for publication

Not applicable.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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